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Short title: Deliveries and perianal Crohn's disease

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ABSTRACT

Background. Despite a high prevalence of Crohn's disease in women of childbearing age, disease-related factors that may impact fertility and perianal Crohn's disease after delivery remain unclear.

Methods. Self-administered questionnaires related to childbirth were completed by women with Crohn's disease referred to a single gastroenterology unit. A survival analysis was performed for statistical purposes.

Results. A total of 184 patients were assessed, including 63 nulliparous women. The cumulative probabilities of having a child were 30%, 51% and 72% at the ages of 25, 30 and 35 years, respectively. Women with colonic disease, prior abdominal surgery and perianal disease were less likely to experience childbirth. After a median follow-up of 165 weeks post-delivery, the cumulative probabilities of fistulizing perianal Crohn's disease occurrence were 8%, 12% and 21% at 1, 2 and 5 years following childbirth, respectively. Contrary to a prior history of perianal Crohn's disease and colonic location, mode of delivery was not associated with perianal fistula. An episiotomy in the group of women with prior anal lesions did not result in a higher rate of fistula recurrence.

Conclusion. Perianal Crohn's disease is associated with fewer pregnancies, however perianal fistulas were less affected by obstetric events than their own natural history.

Keywords: deliveries, pregnancy, perianal Crohn's disease, Crohn's Disease

INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory disease of the gastrointestinal tract that typically occurs in patients between 20 and 30 years, with a slightly higher rate of women in high-incidence cases areas.[1] Thus, pregnancy is a common concern of women with CD of childbearing age.

Many studies have focused on the impact of disease activity on pregnancy and vice versa, but few have analysed both childbearing and delivery.[2] Except for a decrease in fertility following an ileal pouch-anal anastomosis, the overall rates of fertility of women with inflammatory bowel disease (IBD) are similar to those observed in the general population.[2-4] A recent systematic review highlighted a decrease in fertility in women with CD related to voluntary childlessness.[5]

Aside from childbirth, both pregnant women and physicians have a fear of anal injuries related to delivery or Crohn's disease.[6] Up to one third of patients with CD will experience either non-fistulizing perianal or fistulizing perianal Crohn's disease as a complication.[7-9] Based on perianal CD outcomes and hypothetical damage of the perineum related to delivery, a recent ECCO consensus largely favoured caesarean section to limit vaginal delivery in cases of perianal CD or rectal involvement.[10] However, these guidelines should be considered with caution because they are based on limited evidence.[11-13] Moreover, previous retrospective series often lack careful perianal CD anal examinations and delivery details.

Given the concern of both patients and physicians, we aimed to identify disease-related factors that preclude onset of pregnancy and perianal CD outcomes following delivery in a large population of women with CD.

METHODS

Study population

All medical records of consecutive patients referred to a single gastroenterology unit over a seven-year period were reviewed. A centralized diagnostic index was used to identify women with a diagnosis of CD. The CD diagnosis was then confirmed based on radiological, endoscopic and/or histologic evidence. Only women with CD of a childbearing age (defined by age at referral between 15 and 45 years old) were included.

A self-administered questionnaire was mailed to the study population. In absence of an answer, a reminder was mailed to the non-responders. Questions specifically focused on Crohn's disease and childbirth and aimed to assess outcomes of each event over time. Because of the retrospective design of the study, we focused on childbirth rather than pregnancy as an irrevocable endpoint.

The following demographic and clinical characteristics of CD were extracted from the questionnaire and double-checked in electronic medical records of the patients: birth date, age at diagnosis, disease extent (including perianal involvement) and behaviour according to the Montreal classification,[14] and previous history of anal or major abdominal surgery. For perianal CD, fistulizing perianal CD was defined by an occurrence of a perianal abscess or any type of fistula that included a low- or high-perianal fistula and recto-vaginal fistula. Non-fistulizing perianal CD was defined by the occurrence of anal ulcers and stenosis.[7] Anal tags were not taken into account. Data were cross-referenced with those of a prospectively recorded database of perineal Crohn's disease.

Regarding obstetric outcomes, all deliveries were recorded. The following was reviewed for each delivery: gestational age, date, number and term of birth, least and greatest birth weights, mode of delivery (vaginal delivery or caesarean section), use

of episiotomy, instrumental delivery (vacuum extraction or forceps), and occurrence of vaginal tears.

The study was approved by the Institutional Review Board of the university hospital of Rennes.

Statistical analysis

Quantitative variables were described as a median and percentile (I.Q.R. for Inter Quartile Range: 25% and 75%). Categorical variables were presented as a number and percent of a cohort. Follow-up was determined by the duration between the date of investigation and date of completion of the last self-administered questionnaire. For childbirth, time to delivery was considered to begin at the mother birthdate and end at the date of the first delivery or last known follow-up. For fistulising perianal CD related to delivery, time to perianal CD occurrence or recurrence was considered to begin at the last delivery and end at the event or last known follow-up. Two events were defined for analyses: (1) childbirth was defined by a delivery during the follow-up period; and (2) occurrence of perianal fistula by the onset of perianal fistula after the last delivery for women without perianal CD before being pregnant or recurrence of perianal CD after the last delivery for a patient with prior history of perianal CD. Events were assessed using a survival analysis. Cumulative probabilities of childbirth and perianal CD onset were estimated using a Kaplan Meier method. To identify predictive factors for each event, a univariate analysis was first performed using a log-rank test. To identify independent predictors of each events by multivariate analysis, all significant variables with p-values <0.05 in the log-rank test were retained and integrated into a Cox proportional hazards regression model. The results are shown as HRs with 95% CIs. Statistical analyses were performed using JMP® Pro 10.0.0 software (Cary, North Carolina, USA).

RESULTS

Study population at referral

Of the 329 women referred for Crohn's disease during the study period and of childbearing age, 2 patients had died (0.6%), 105 declined to complete the questionnaire (31.9%), and 38 were lost to follow-up (11.5%). Thus, our study population was composed of 184 patients (55.9%). The characteristics of the study population regarding Crohn's disease and childbirth are listed in Table 1.

Of the 184 women, 121 had at least one delivery (65.7%). Of these 121 patients, the median age at CD diagnosis was 27 years (range 12-57) and at first childbirth 25.5 years (range 18-37). The median age at the end of follow-up was 41 years (range 26-61). According to the Montreal classification,[14] disease locations were ileal, colic and ileocolic for 23 (19%), 59 (48.7%) and 36 women (29.7%), respectively. Twenty-six of the 121 patients (21.5%) had perianal CD prior to childbearing, and 51 women (42.1%) developed perianal CD during follow-up. Major abdominal surgery was required for 39 women during the follow-up period (32%).

Of the 63 childless women, median age at CD diagnosis was 19 years (range 3-44). Disease locations were ileal, colic and ileocolic for 10 (15.9%), 20 (31.7%) and 29 women (46%), respectively. A total of 37 patients developed perianal CD (58.7%). Major abdominal surgery was required for 32/63 women during follow-up (50.8%). The characteristics of the pregnant women before delivery and the childless women are summarized in supplementary Table S1.

Childbirth and associated factors

Overall, the cumulative probabilities of a first delivery at the ages of 20, 25, 30 and 35 years were 14%, 30.2%, 50.8% and 71.6%, respectively (Figure 1A).

The results of the univariate analysis indicated that the disease location, known diagnosis of Crohn's disease (prior to pregnancy), major abdominal surgery and perianal CD were associated with fewer childbirths as shown in Table 2.

The results of the multivariate analysis showed that the women with an L2 disease location (ileal), prior abdominal surgery or perianal Crohn's disease before childbearing were considerably less likely to become pregnant (Table 2 and Figure 1 panels B, C, D). The occurrence of pregnancy was similar regardless of the type of perianal CD and location of abdominal surgery. Of the women with perianal CD before childbearing, the median age at the first childbirth was 27, and the cumulative probabilities of having a delivery were 6.5%, 15.1%, 28.5% and 45.9% at the ages of 20, 25, 30 and 35 years, respectively.

Fistulizing perianal CD following delivery and associated factors

Of the 121 CD women who had undergone childbirth, 45 (including 12 women with perianal CD prior to pregnancy) developed a perianal fistula following delivery (37.2%) after a median time of 165 weeks (range 28-485). Fistulizing perianal CD occurred following the first delivery in 16 women, second delivery in 21 women, third delivery in 5 women and fourth delivery in 3 women. The cumulative probabilities of fistula onset/recurrence after childbirth were 7.6%, 12%, 15.5% and 21.4% at 1, 2, 3 and 5 years, respectively (Figure 2A).

The overall caesarean section and episiotomy rates for the patients are shown in Table 1. In the 45 women who developed fistulizing perianal CD after their last childbirth, the mode of delivery was a caesarean section for 24 (53.3%) patients and

vaginal delivery with episiotomy (with or without instrumental extraction) and/or perianal tears for 10 (22.2%).

The women with L1 disease were less likely to develop a perianal fistula, as shown in Table 3. Conversely, L2 disease, colonic resection before childbearing and a diagnosis of perianal CD prior to pregnancy were associated with a higher risk of perianal fistula following childbirth. The occurrence of perianal fistula was not impacted by the mode of delivery, which included episiotomy, perianal tears and instrumental delivery. The multivariate analyses results showed that a previous diagnosis of perianal CD and colonic CD location independently increased the risk of perianal CD occurrence (Figure 2B and Table 3). The severity of perianal CD in the women following an episiotomy was similar to those without an episiotomy in regards to the need for anal surgery (27% and 37%, respectively, p=0.23), number of anal surgeries after the diagnosis of fistulizing perianal CD (0.6 and 0.8%, respectively, p=0.42) and need for a permanent stoma (8% and 7%, respectively, p=0.56). Focusing on vaginal delivery, the perianal CD occurrence after childbirth was not associated with an episiotomy (Figure 3A). The severity of perianal CD following an episiotomy was similar to those without an episiotomy concerning the need for anal surgery (27% and 37%, respectively, p=0.23), number of anal surgeries after the diagnosis of fistulizing perianal CD (0.6% and 0.8%, respectively, p=0.42) and need for a permanent stoma (8% and 7%, respectively, p=0.56). A total of 26 women had perianal CD before delivery. Perianal CD was in remission without active clinical lesions before delivery for 19 women. Seven women experienced active fistulizing disease during pregnancy. Of these 7 patients, 5 underwent C-section, and 2 had a vaginal delivery without an episiotomy or perianal tears. At the end of the follow-up, 3 of the 7 women required a permanent stoma. These 3 women had a C-section.

Based on the history of perianal CD before childbirth, the subgroup analysis did not find any difference in outcomes after an episiotomy (figure 3B and 3C). Similar results were observed for a vaginal delivery when the diagnosis of CD occurred after childbirth. During the follow-up, 22 patients developed a recto-vaginal fistula. Similarly, the mode of delivery did not affect the rate of rectovaginal fistula formation. The presence of a rectovaginal fistula was positively associated with the colonic location of CD (HR=2.83 [1.02-9.01], p=0.0442).

DISCUSSION

Pregnancy remains a challenging issue for both a treating physician and a woman with CD, a disease that may result in childlessness.[5] The reasons for voluntary childlessness in women with CD remain unclear. Several patient-related factors have been suggested, such as a fear of disease outcomes during pregnancy, fear of IBD inheritance, fear of infertility and educational background.[5, 6, 15, 16] None of these studies took into account disease-related factors. We identified important factors related to CD that directly impact the onset of childbirth. Surprisingly, a prior diagnosis of CD was not associated with childlessness. By contrast, abdominal surgery, colonic CD location and perianal CD before the onset of childbirth highly decreased the fertility in this population. Although, in some cases, surgery could decrease the fertility of women, both factors are known to be associated with a disabling course of CD. These results underline the possible influence of a physician's advice to delay conception because of the severity of CD, not the presence of CD itself. Fear of women could be another associated explanation: they previously experienced surgery for perianal CD and knew its impact on quality-of-life and disability.

One might argue that improved knowledge on CD outcomes during and after delivery may be a prerequisite to having children. Overall, the risk of perianal CD following delivery was low. Five years after delivery, about one fifth of women developed perianal CD. In the literature, the rate of perianal CD after childbirth ranges from 0% to 67%.[11, 12, 17, 18] We did not restrict perianal CD occurrence within the two years of the post-partum to avoid misdiagnosis of late onset of perianal CD related to childbirth scars. None of factors related to childbirth were associated with the occurrence of fistulizing perianal CD by the univariate or the multivariate analyses. By contrast, the disease characteristics already known to increase the risk of perianal CD, such as colonic disease or prior perianal CD, were associated with the occurrence of perianal CD.

The rate of caesarean sections was similar to that observed in previous studies[12, 18] and tended to be higher compared to the general population. A total of 39% of the women required a caesarean section compared to an overall rate of 20.7% in a referral hospital in France.[19] Importantly, a caesarean section did not protect against the onset or recurrence of perianal CD in the present study, which highlights the high risk of perianal CD relapse and low risk of perianal CD onset regardless of the mode of delivery. Importantly, a vaginal delivery with or without perineal tears or an episiotomy was not associated with the occurrence of perianal CD after delivery, even in the patients with a prior history of perianal lesions. This is in line with recent data from the Netherlands that did not show any association between perianal CD and mode of delivery.[18] Moreover, the authors underlined the overall increased risk for complications following a caesarean section.[18] In a retrospective study from Manitoba, unless there was a high rate of perianal trauma related to vaginal delivery, the rate of active perianal CD following childbirth remained low.[12] Brandt et al

observed that 18% of perianal CD onset following vaginal delivery was within 2 months of delivery. However, the authors admitted methodological limitations, particularly the lack of data verification. Additionally, no CD characteristics were taken into account.[11] Finally, the present study underlined the link between perianal CD and CD characteristics rather than obstetric choice.

Our study results should be interpreted with caution for several reasons. First, this is a retrospective study based on self-administered questionnaires. While CD data were double-checked in the chart of the patients (which were prospectively recorded, especially regarding perianal CD), some data regarding the pregnancy and delivery could not be verified. To overcome this limitation, we excluded all subjective data from the analyses, such as the reason for the mode of delivery. This referral centre study introduces a recruitment bias with severe CD more able to develop perianal lesions. Finally, the population of childless women was younger and more severe, as underlined by the rate of perianal CD and abdominal surgery. That said, the main strengths of this work are its sample size, long duration of follow-up, choice of survival analysis to limit impact of age, follow-up duration and systematic assessment of perianal CD in an IBD unit. Most of the data related to IBD were recorded in a prospective database using recommended classifications and validated scales, such as the Montreal classification of the luminal disease and different anal phenotypes.

In conclusion, perianal CD and abdominal surgery severely affect fertility. The age onset of first childbirth was delayed by approximately 5 to 7 years. By contrast, the mode of delivery in childbearing women did not appear to impact the natural history of perineal Crohn's disease, which should reassure mothers and physicians following vaginal delivery.

Conflict of interest:

GB received lecture fees from Abbvie, Ferring and MSD, LS received lecture Fees from Abbvie, JFB received lecture fees from Abbvie. AG, JL and PP déclares no conflict of interest.

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FIGURE LEGENDS

Figure 1:

Panel A. Cumulative probabilities of first childbirth

Panels B-D. Kaplan-Meier analysis of first childbirth according to the predictors identified at multivariate analysis

Panel B. Disease location (HR [L2] 0.50, 95% CI [0.31-0.85], p=0.01)

Panel C. Abdominal surgery prior to childbirth (HR=0.19, 95% CI [0. 01-0. 36], p< 0.0001)

Panel D. Perianal Crohn's disease prior to childbirth (HR=0.31, 95% CI [0.20-0.49], p<0.0001).

CD, Crohn's disease; HR, Hazard Ratio; L1, ileal location; L2, colic location; L3, ileocolic location.

Figure 2:

Panel A. Cumulative probability of perianal Crohn's disease (perianal CD) after childbirth

Panel B. Kaplan-Meier analysis according to perianal Crohn's disease diagnosed before childbearing (HR=2.82 CI95[1.37-4.5], p=0.0057

Panel C. Kaplan-Meier analysis according to Crohn's disease location (HR=3.32 CI95[1.28-11.31], p=0.01).

CD, Crohn's disease; HR, Hazard Ratio.

Figure 3:

Panel A. Perianal Crohn's disease following an episiotomy in the whole study population (log-rank, p=0.06)

Panel B. Perianal Crohn's disease in women without perianal Crohn's disease before childbearing (log-rank, p=0.06)

Panel C. Perianal Crohn's disease in women with prior history of perianal Crohn's disease (log-rank, p=0.42).

CD, Crohn's disease.

Table 1. Demographic and laboratory features of the patients with type 1 gastric carcinoid (GC1), non recurrent GC1, at the time of first diagnosis, and recurrent GC1, at the moment of first recurrence. There were no significant differences among recurrent and non-recurrent GC1 patients.

Parameter	GC1 (n=25)	Non recurrent GC1 (n=13)	Recurrent GC1 (n=12)
Gender (M, %)	5 (20)	1 (0.7%)	4 (33%)
Age [median (range), years]	62 (35-82)	61 (35-82)	65 (51-80)
Anti-parietal cell antibodies	20 (80%)	9 (69%)	11 (92%)
BMI [median (range), kg/m^2]	22 (18-35)	22 (18-35)	22 (20-23)
Gastrin [median (range), pg/mL]	899 (139-2820)	894 (340-2110)	802 (171-2003)
Chromogranin A [median (range), U/L]	44 (15-230)	57 (16-230)	33 (14-72)
Follow-up [median (range), months]	77 (6-165)	58 (6-165)	94 (42-165)
GC1 Diameter [median (range), mm]	6 (2-30)	8 (2-14)	4 (1-10)
GC1 Grade (Ki-67 <2/Ki-67 2-20)	23/2	11/2	12/0
ECL hyperplasia [n, (%)]			
Absent	4 (16)	1 (8)	1 (8)
Simple	1 (4)	1 (8)	3 (25)
Linear	2 (8)	2 (15)	2 (17)
Micronodular	10 (40)	7 (54)	4 (33)

Macronodular		8 (32)	2 (15)	2 (17)
Intestinal metaplasia	[n, (%)]	18 (72)	9 (69)	12 (100)
Other tumors	[n, (%)]	5 (20)	3 (23)	2 (17)

GC1, type 1 gastric carcinoid; BMI, body mass index; ECL, enterochromaffin-like cells

Table 2. Association between chronic liver disease mortality (overall and by etiology) and education level: Odds Ratio with 95% Confidence Interval estimated by conditional logistic regression. Veneto region, 2011-2013.

		Middle vs. High/college	Primary vs. High/college
	Number of deaths	OR (CI) [#]	OR (CI) [#]
Males			
All liver diseases	2,023	1.31 (1.12 – 1.53)	1.37 (1.18 – 1.60)
Alcohol-related	544	1.32 (0.98 – 1.77)	1.62 (1.22 – 2.14)
Virus-related	323	1.28 (0.93 – 1.76)	0.75 (0.53 – 1.05)
NVNA*	1,198	1.36 (1.10 – 1.69)	1.49 (1.22 – 1.82)
Females			
All liver diseases	768	1.35 (0.99 – 1.84)	1.72 (1.29 – 2.30)
Alcohol-related	141	1.24 (0.63 – 2.46)	2.34 (1.23 – 4.45)
Virus-related	171	1.30 (0.69 – 2.44)	1.24 (0.69 – 2.22)
NVNA*	466	1.41 (0.94 – 2.12)	1.77 (1.22 – 2.59)

[#] Odds Ratio with 95% Confidence Interval

NVNA, non-virus/non-alcohol related

Table 3 Factors associated with fistulizing perianal Crohn's disease occurrence after childbirth

	UNIVARIATE ANALYSIS	MULTIVARIATE ANALYSIS
VARIABLES	p-value	HR [95% CI], p-value
Age at CD diagnosis – Montreal classification	0.516	
Montreal A1 (<16)	0.80816	
Montreal A2 (17-39)	0.7988	
Montreal A3 (>39)	0.7216	
Montreal L1 (ileal)	0.0168	reference
Montreal L2 (colic)	0.0079	3.32 [1.28-11.31], 0.01
Montreal L3 (ileocolic)	0.3051	1.82 [0.60-6.73], 0.29
Diagnosis of CD before childbirth	0.3689	
Abdominal surgery prior to childbirth	0.2002	
Ileal resection	0.9529	
Colonic resection	0.0176	2.43 [0.66-7.19], 0.16
Perianal CD prior childbirth	<0.0001	2.82 [1.37-4.5], 0.0057
Number of childbirths per patient	0.8229	
Birth Weight		
Lowest	0.9025	
Highest	0.2992	
Mode of delivery		
Caesarian section	0.1076	
Episiotomy	0.0662	

A, Age; CD, Crohn's Disease; IQR, Interval Quartile Range; L, location; HR, hazard ratio; CI, confidence interval

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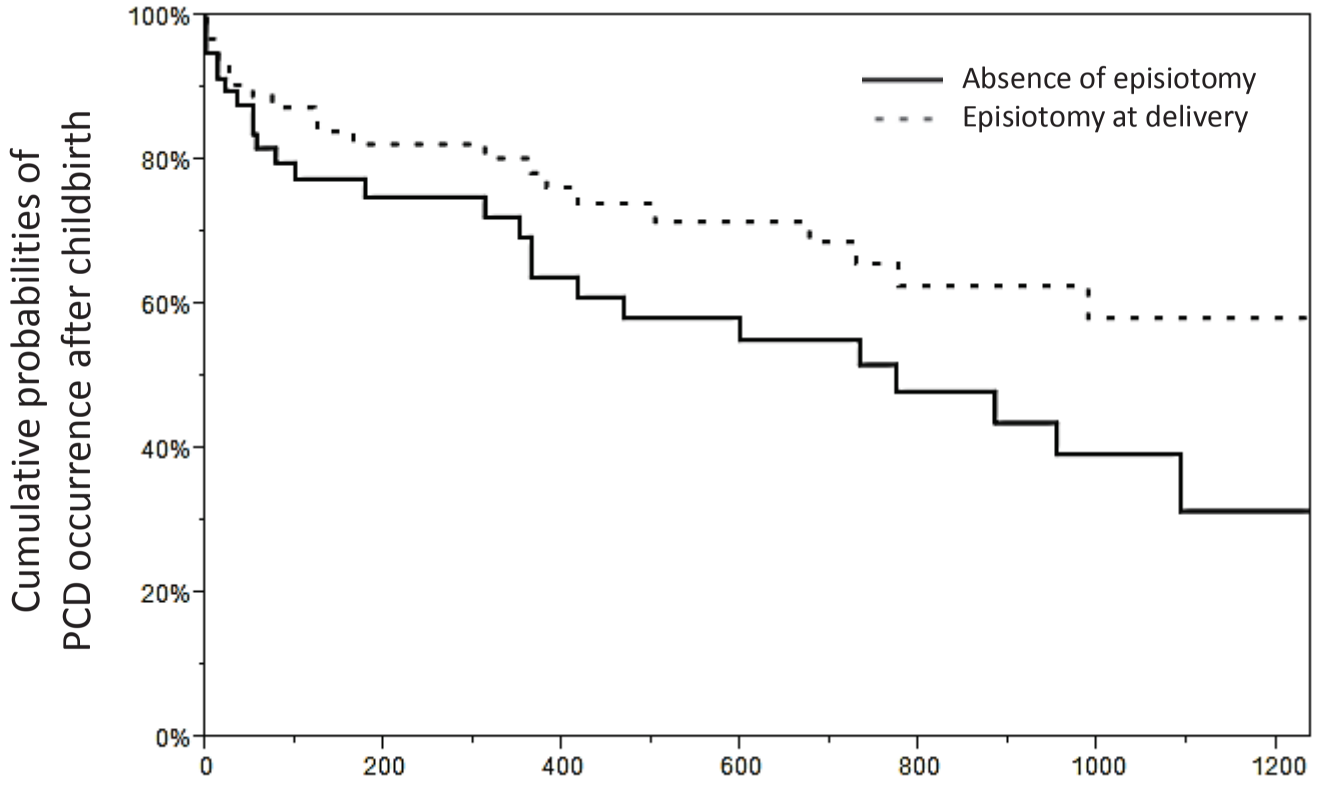
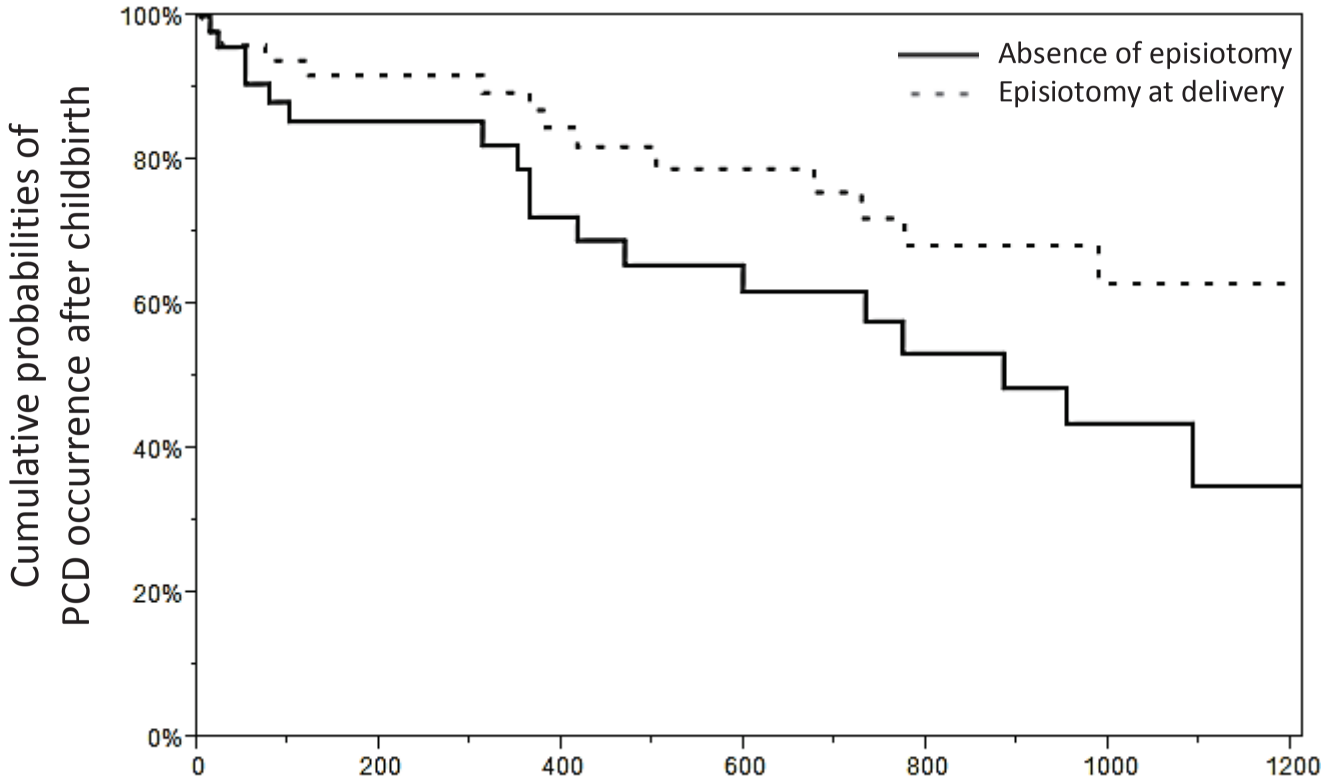


At risk								
No Episiotomy	**58**	**36**	**30**	**22**	**18**	**13**	**8**	**2**
Episiotomy	63	52	42	30	26	20	11	7

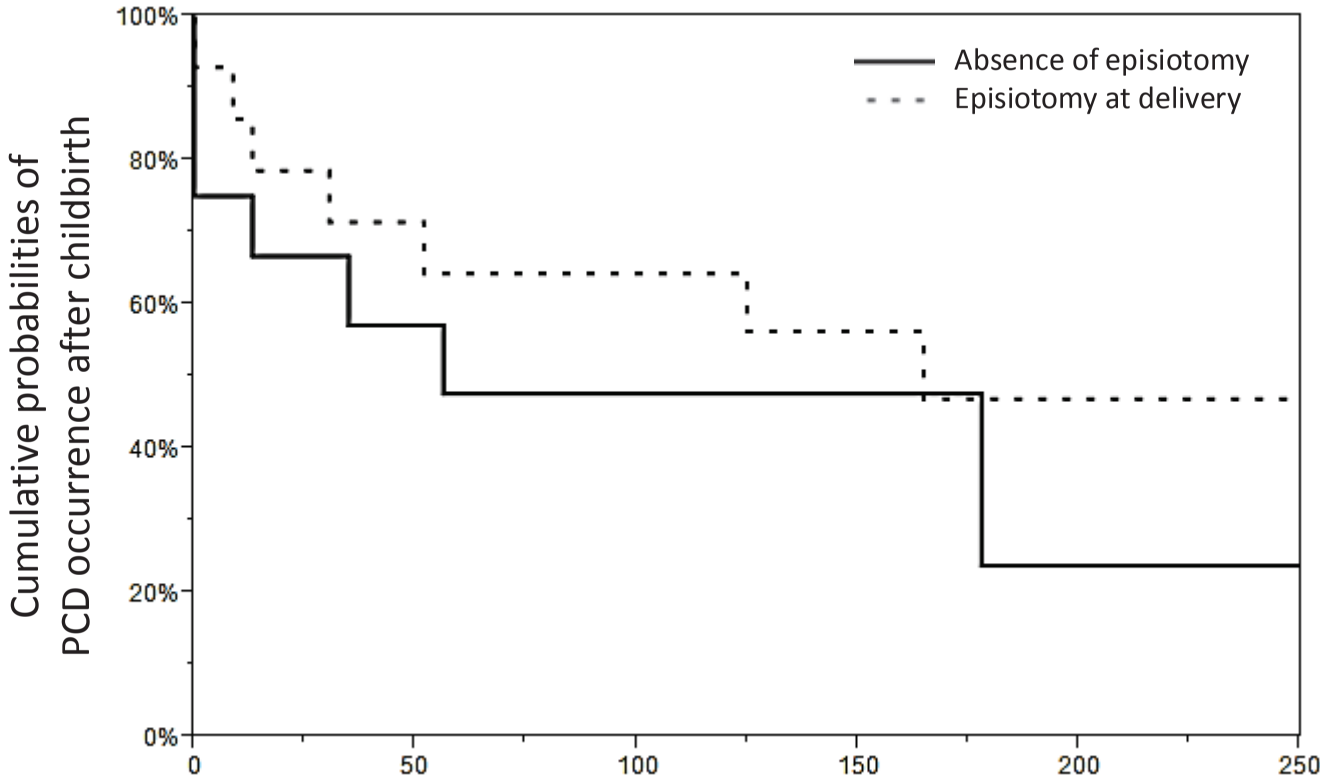
Figure 3A



At risk

No Episiotomy	**46**	**31**	**29**	**19**	**17**	**12**	**8**	**4**
Episiotomy	49	44	38	28	25	18	12	6

Figure 3B



At risk						
No Episiotomy	**12**	**7**	**5**	**4**	**2**	**2**
Episiotomy	14	11	9	7	6	6

Figure 3C

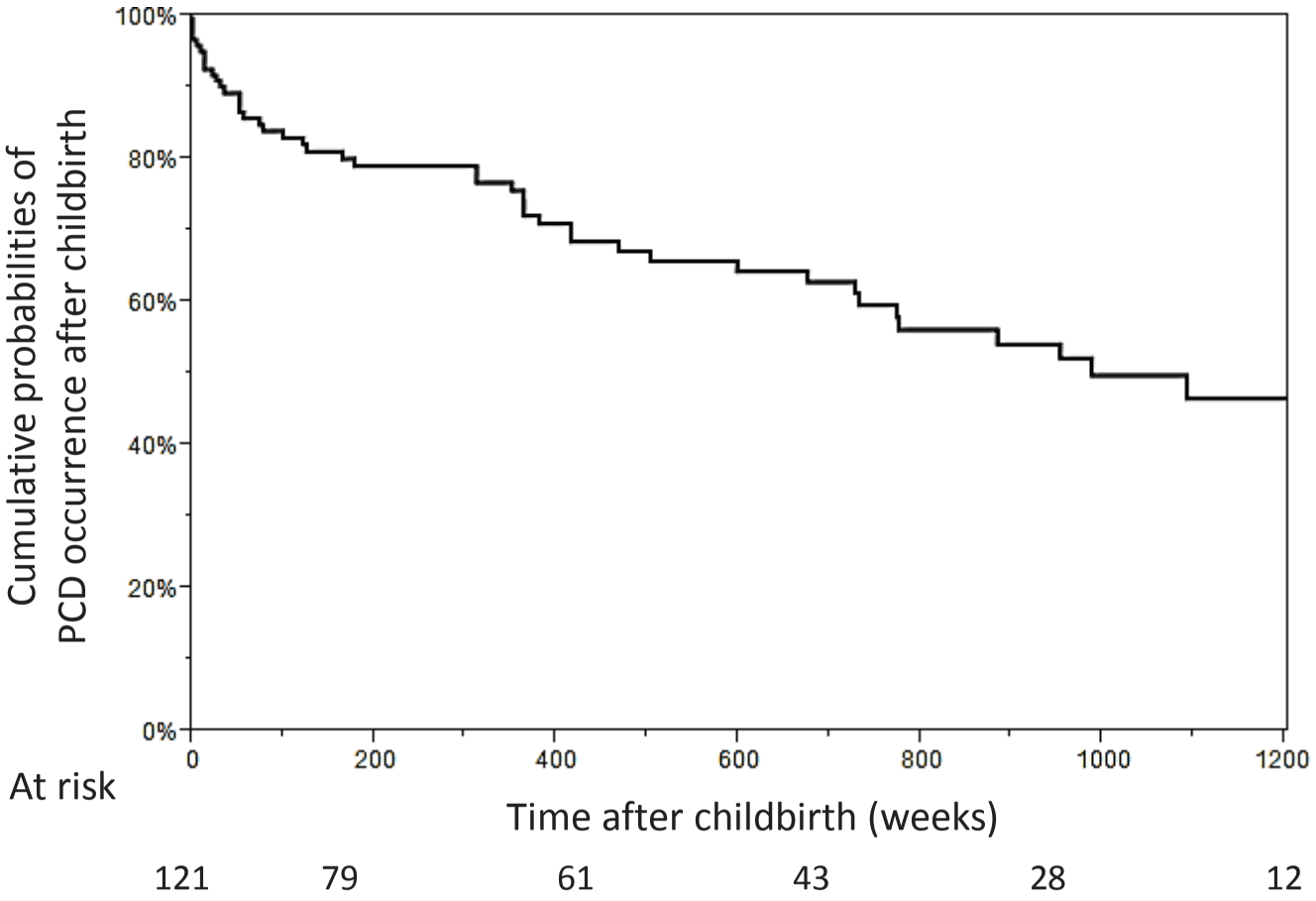
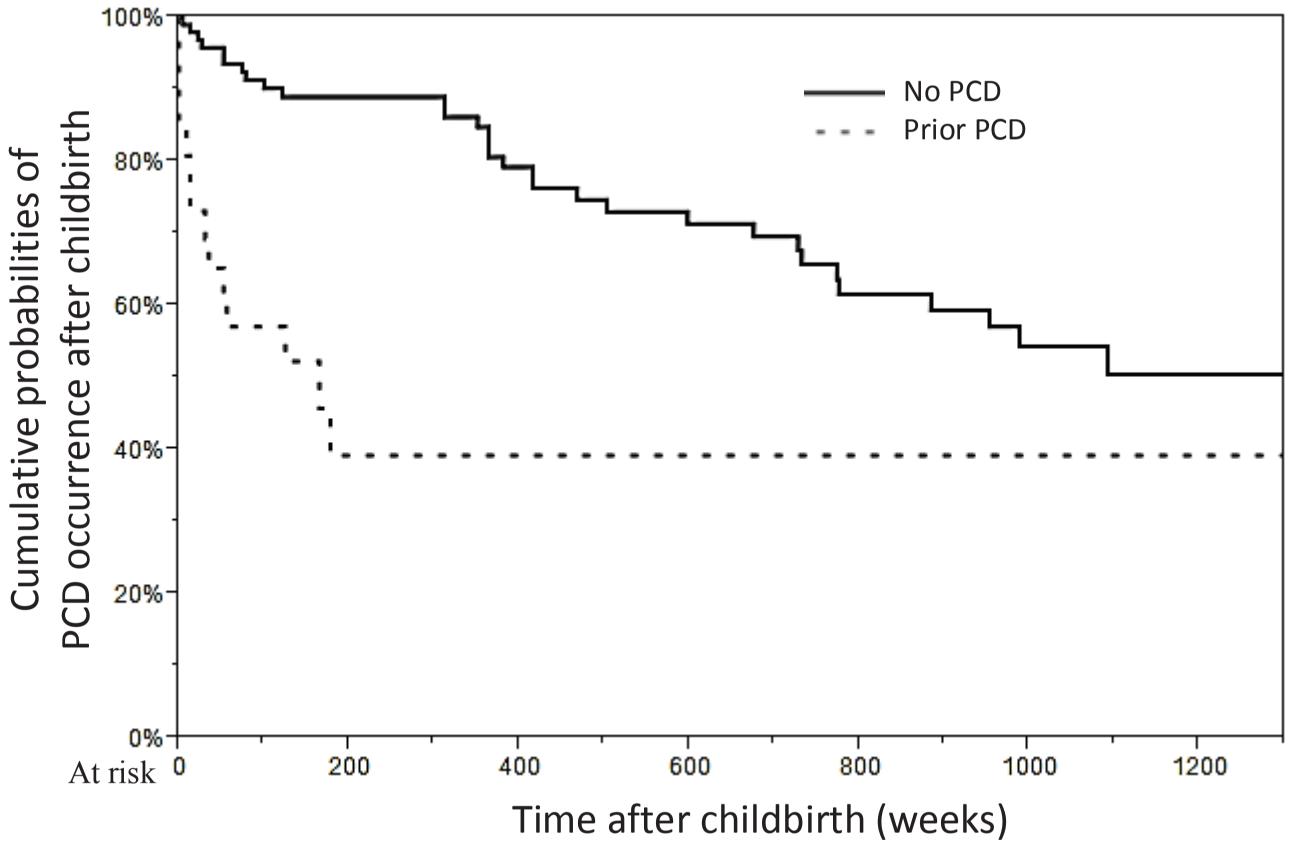
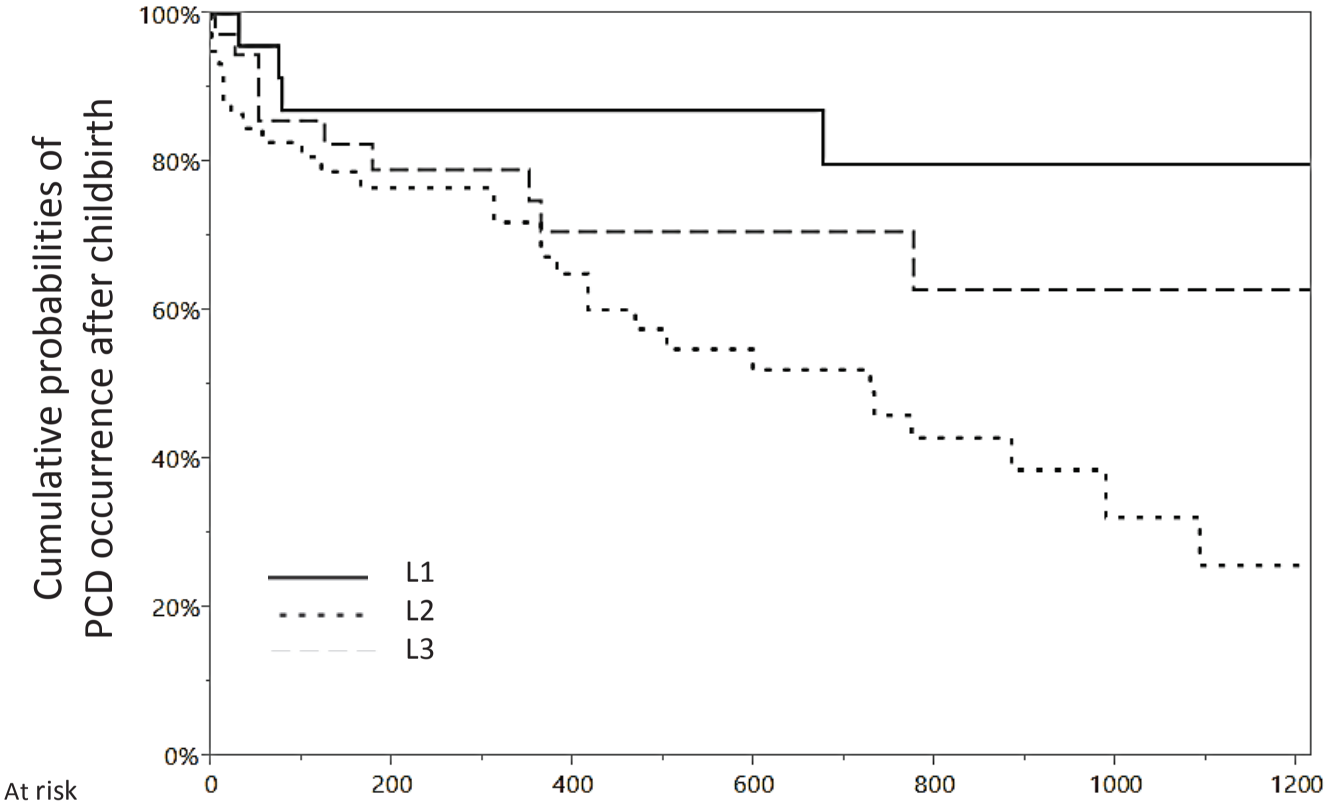

Cumulative probabilities of PCD occurrence after childbirth
100%
80%
60%
40%
20%
0%
0
200
400
600
800
1000
1200
Time after childbirth (weeks)
At risk
121
79
61
43
28
12

Figure 2A



No PCD	**95**	**75**	**64**	**46**	**39**	**27**	**14**	**8**
Previous PCD	26	11	6	4	4	3	3	3

Figure 2B



At risk						
L1	**23**	**17**	**15**	**12**	**10**	**5**
L2	59	35	28	20	10	5
L3	36	23	17	13	9	5

Figure 2C

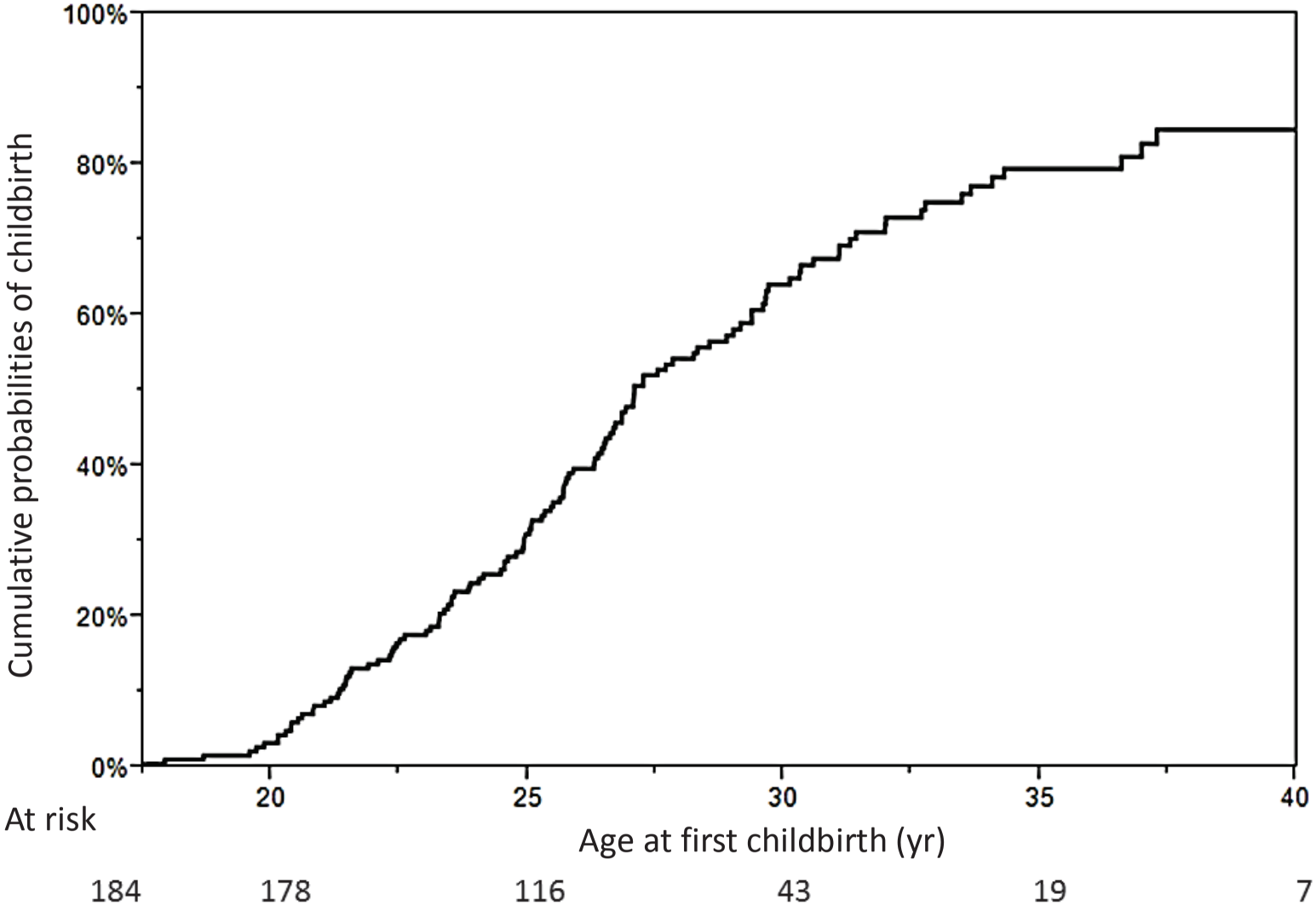
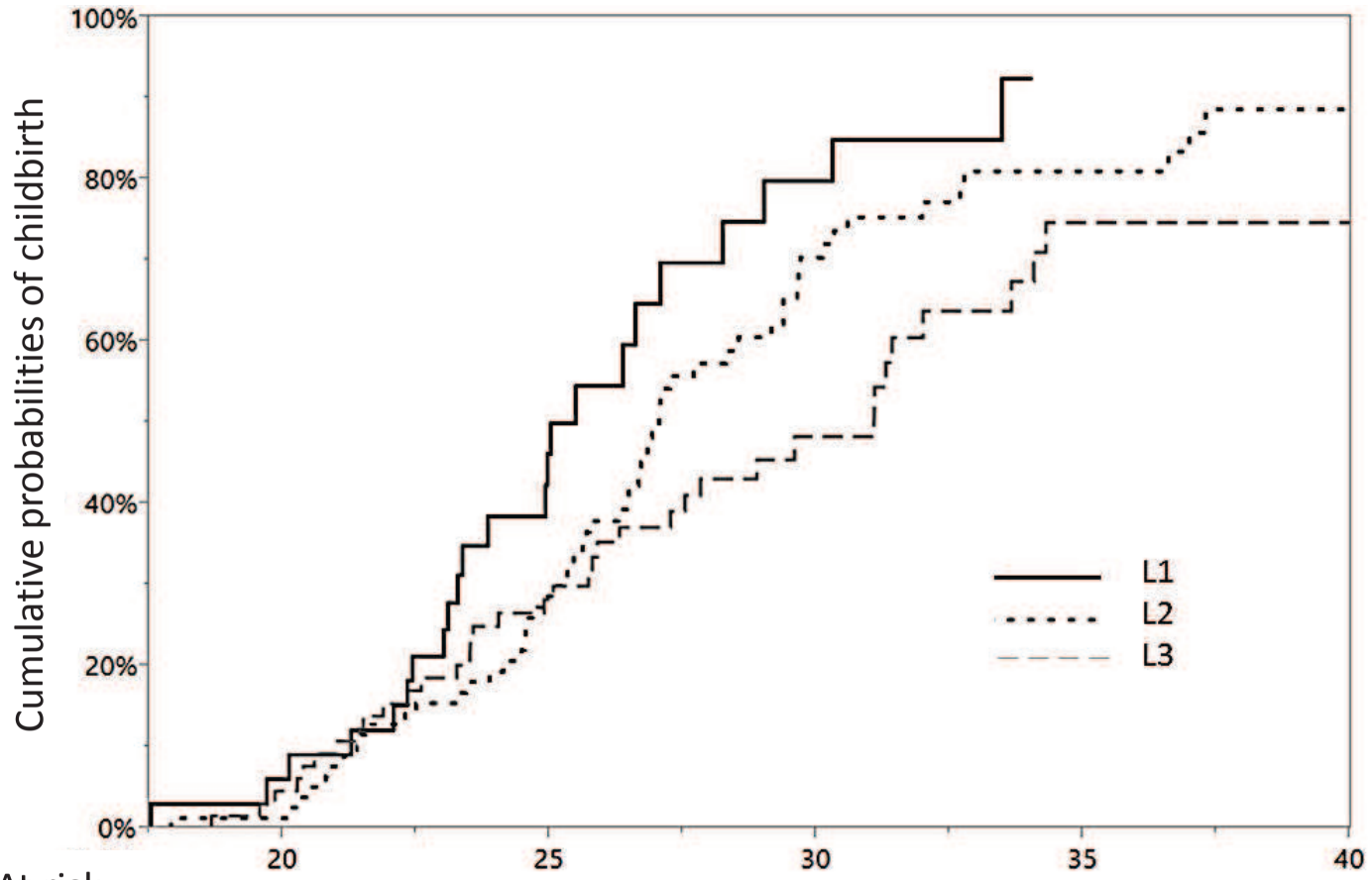
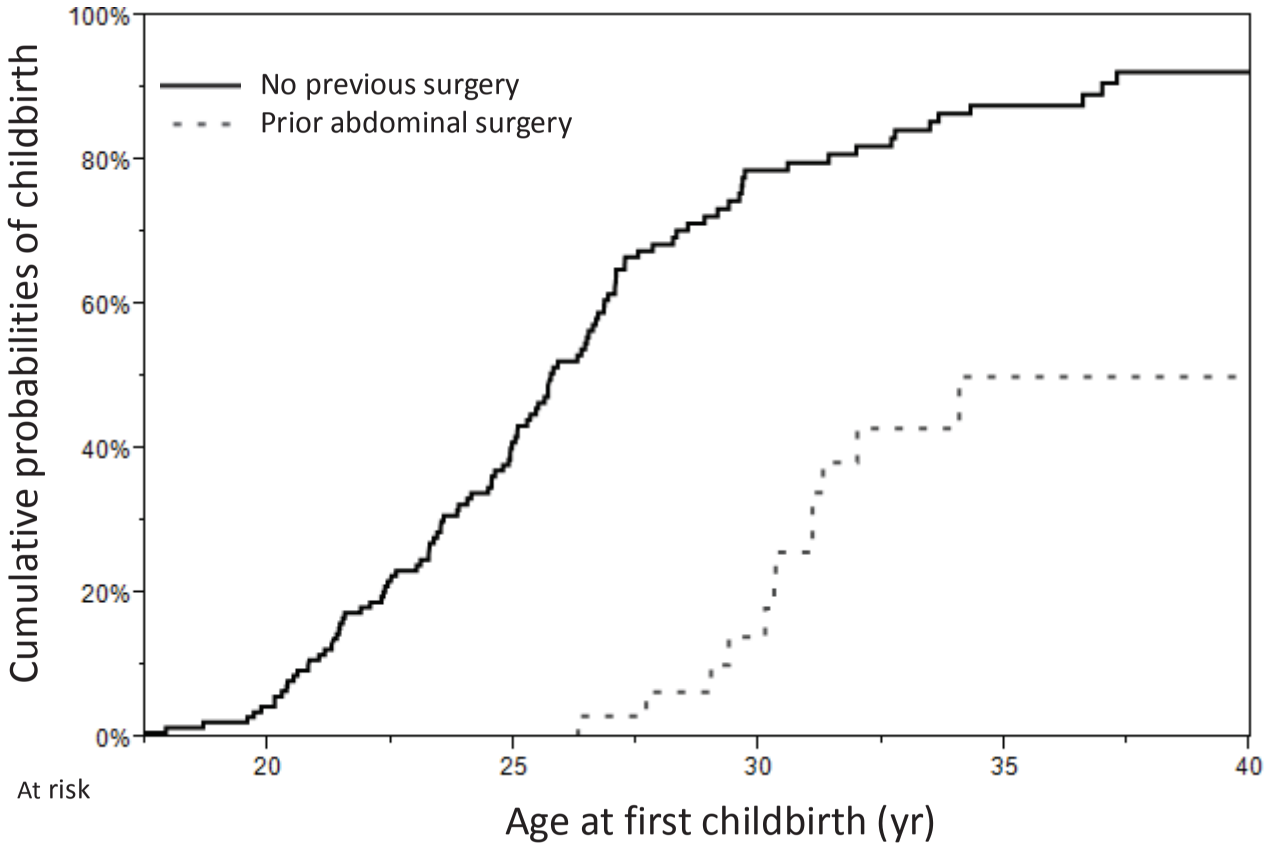

100%
80%
60%
40%
20%
0%
Cumulative probabilities of childbirth
20
25
30
35
40
Age at first childbirth (yr)
At risk
184
178
116
43
19
7

Figure 1A



At risk								
L1	**33**	**31**	**26**	**10**	**4**	**2**	**0**	**0**
L2	79	78	66	34	19	10	7	4
L3	65	63	53	35	19	10	6	4

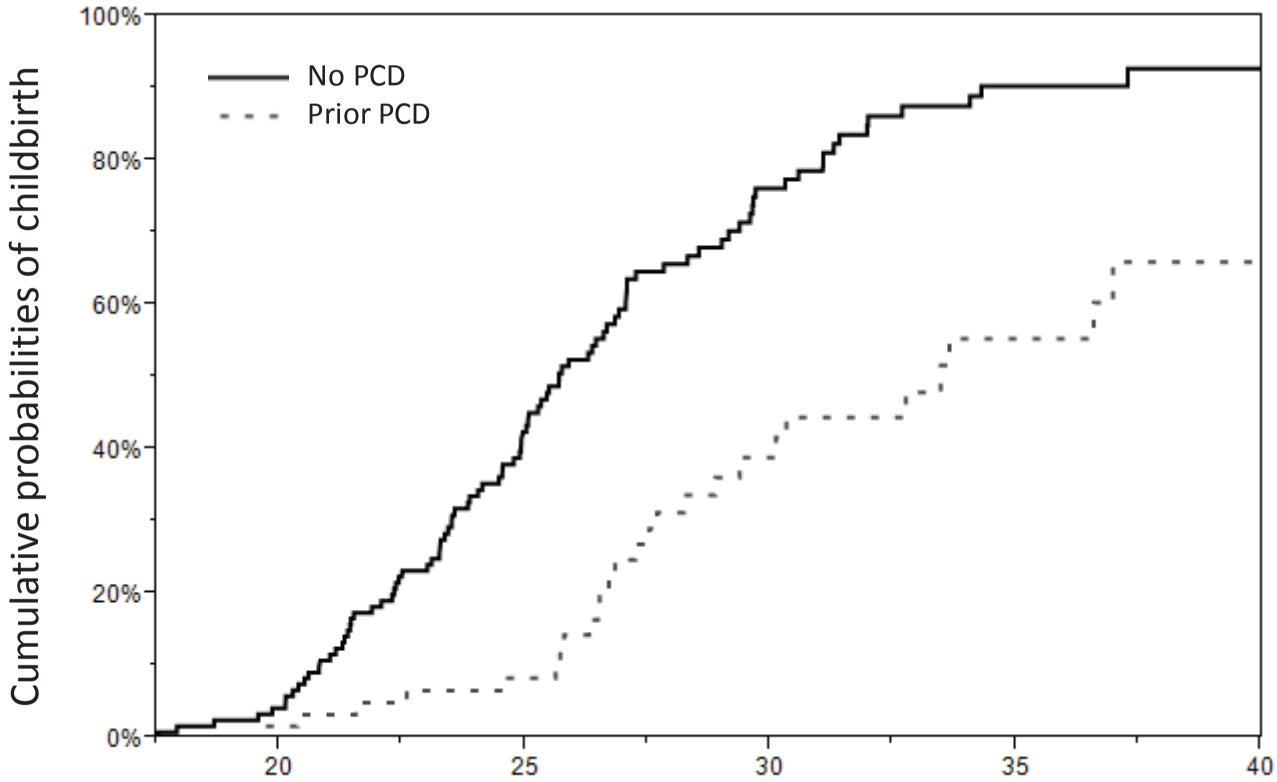
Figure 1B



At risk

No surgery	**140**	**134**	**104**	**47**	**20**	**15**	**8**	**6**
Previous surgery	44	44	44	33	23	11	5	2

Figure 1C



At risk								
No PCD	**121**	**117**	**93**	**50**	**21**	**11**	**5**	**3**
Previous PCD	63	62	56	41	23	17	9	5

Figure 1D